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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: DESLORATADINE PATENT LITIGATION	MDL No. 1851 Civil Action No. 07-03930-MLC-TJB
SCHERING CORPORATION, Plaintiff, v. ZYDUS PHARMACEUTICALS, USA, INC., et al. Defendants.	Civil Action No. 06-4715-MLC-TJB This Filing Applies To: Civil Action No. 08-CV-3260 (MLC)(TJB) (Consolidated Case) **DOCUMENT ELECTRONICALLY FILED**

ANSWER, DEFENSES, AND COUNTERCLAIMS OF SANDOZ INC. TO SCHERING CORPORATION'S COMPLAINT

Sandoz Inc. ("Sandoz") responds to the numbered paragraphs of the Complaint ("Complaint") filed by Schering Corporation ("Schering") as follows:

1.A. Sandoz lacks knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 1.A and therefore denies those allegations.

1.B. Sandoz admits that it is a corporation having a place of business at 506 Carnegie

Center, Princeton, New Jersey 08540, and denies the remaining allegations in paragraph 1.B.

2. Sandoz admits that the Complaint purports to state a cause of action against Sandoz for infringement of United States Patent No. 6,100,274 ("the '274 patent") under 35 U.S.C. § 271(e)(2)(A). Sandoz denies the remaining allegations in paragraph 2.

3. Sandoz makes no answer to the allegations in paragraph 3 to the extent those allegations state legal conclusions rather than facts. To the extent an answer is required, Sandoz admits the Court has subject matter jurisdiction over the action against Sandoz. Sandoz denies the remaining allegations in paragraph 3.

4. Sandoz makes no answer to the allegations in paragraph 4 to the extent those allegations state legal conclusions rather than facts. To the extent an answer is required, Sandoz admits this Court has personal jurisdiction over Sandoz. Sandoz denies the remaining allegations in paragraph 4.

5. Sandoz makes no answer to the allegations in paragraph 5 to the extent those allegations state legal conclusions rather than facts. To the extent an answer is required, Sandoz admits that venue in this judicial district is proper. Sandoz denies the remaining allegations in paragraph 5.

6. Sandoz admits the '274 patent has printed on its face an issue date of Aug. 8, 2000, the indicated title of the patent, and Schering Corporation as assignee. Sandoz denies the remaining allegations in paragraph 6.

7. Sandoz admits that it submitted Abbreviated New Drug Application ("ANDA") No. 90-127 to the FDA after June 21, 2006 seeking FDA approval for the desloratadine/pseudoephedrine tablet product that is the subject of ANDA 90-127 ("Sandoz ANDA Product") prior to the expiration of the '274 patent. Sandoz denies the remaining

allegations in paragraph 7.

8. Sandoz admits that ANDA 90-127 includes a certification that the claims of the '274 patent are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of the Sandoz ANDA Product, and that Sandoz provided written notification of ANDA 90-127 to Schering. Sandoz denies the remaining allegations in paragraph 8.

9. Sandoz makes no answer to the allegations in paragraph 9 to the extent those allegations state legal conclusions rather than facts. To the extent an answer is required, Sandoz denies the allegations in paragraph 9.

10. Sandoz denies the allegations in paragraph 10.

AFFIRMATIVE DEFENSES

Sandoz sets forth the following affirmative defenses and does not intend to limit thereby Sandoz's ability to seek to allege any and all defenses not presently known that are revealed during the course of discovery in this case.

First Affirmative Defense

Sandoz has not infringed, is not infringing, and will not infringe any valid and enforceable claim of U.S. Patent No. 6,100,274.

Second Affirmative Defense

Sandoz has not, does not, and will not induce or contribute to any infringement of any valid and enforceable claim of U.S. Patent No. 6,100,274, and is not liable for any act that would be construed as any form of infringement of that patent.

Third Affirmative Defense

U.S. Patent No. 6,100,274, and each claim thereof, is invalid for failing to comply with the requirements of the Patent Laws of the United States, specifically 35 U.S.C. § 101 *et seq.*

Fourth Affirmative Defense

The Complaint fails to state a claim upon which relief may be granted, including but not limited to any claim under 35 U.S.C. § 271 (a), (b) and (c).

COUNTERCLAIMS

1. This is a declaratory judgment action seeking declarations of noninfringement and invalidity of United States Patent No. 6,100,274 and a declaration of noninfringement of United States Patent No. 6,979,463.

FIRST COUNTERCLAIM
(DECLARATION OF NONINFRINGEMENT OF U.S. PATENT NO. 6,100,274)

2. Sandoz Inc. ("Sandoz") brings this counterclaim pursuant to the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, and pursuant to the Patent Laws of the United States, 35 U.S.C. § 101 *et seq.*

3. Sandoz is a corporation organized and existing under the laws of the state of Colorado having a place of business at 506 Carnegie Center, Princeton, New Jersey 08540.

4. Upon information and belief, Schering Corporation ("Schering") is a New Jersey corporation having places of business throughout New Jersey, including a place of business at 3070 Route 22 West, Branchburg, New Jersey 08876.

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

6. This Court has personal jurisdiction over Schering by virtue of, *inter alia*: (1)

Schering's filing of the Complaint against Sandoz in this case; (2) Schering's presence in New Jersey; and (3) Schering's systematic and continuous contacts with New Jersey.

7. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

8. Schering has charged Sandoz with infringement of U.S. Patent No. 6,100,274 ("the '274 patent") based upon Sandoz's filing with the FDA of Abbreviated New Drug Application ("ANDA") No. 90-127, seeking to obtain approval to engage in commercial manufacture, use and sale of the desloratadine/pseudoephedrine tablet product that is the subject of ANDA 90-127 ("Sandoz ANDA Product") prior to expiration of the '274 patent.

9. Sandoz has asserted that the Sandoz ANDA Product has not infringed, is not infringing and will not infringe any valid claim of the '274 patent and has further asserted that the '274 patent is invalid.

10. There is a justiciable case or controversy between Sandoz and Schering with respect to the validity and infringement of the '274 patent.

11. The Sandoz ANDA Product has not infringed, is not infringing and will not infringe any valid claim of the '274 patent.

SECOND COUNTERCLAIM
(DECLARATION OF INVALIDITY OF U.S. PATENT NO. 6,100,274)

12. Sandoz realleges all of the foregoing paragraphs of its counterclaims as if set forth specifically herein.

13. The '274 patent is invalid for failing to comply with the requirements of the Patent Laws of the United States, specifically 35 U.S.C. § 101 *et seq*.

THIRD COUNTERCLAIM
(DECLARATION OF NONINFRINGEMENT OF U.S. PATENT NO. 6,979,463)

14. Sandoz realleges all of the foregoing paragraphs of its counterclaims as if set forth specifically herein.

15. Upon information and belief, Schering is the owner of U.S. Patent No. 6,979,463 ("the '463 patent"), a copy of which is attached hereto as Exhibit A, and has the right to sue for infringement of the '463 patent.

16. Upon information and belief, Schering is the holder of New Drug Application ("NDA") No. 21-605 for the desloratadine/pseudoephedrine tablets described therein, which are marketed as Clarinex-D® 24 Hour tablets ("the Schering NDA 21-605 Product").

17. As the holder of the NDA for the Schering NDA 21-605 Product, Schering has been and is required to file certain patent information with the FDA. In particular, Schering has been and is required to file with the FDA the patent number and expiration date of any patent which claims the drug for which the applicant submitted the NDA or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. 21 U.S.C. § 355(b)(1) and (c)(2).

18. The FDA publishes the patent information provided by an NDA holder such as Schering in the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as the Orange Book.

19. Upon information and belief, Schering filed patent information with the FDA for both the '274 patent and the '463 patent, causing the FDA to list both the '274 patent and the '463 patent in the Orange Book for the Schering NDA 21-605 Product.

20. On or about November 15, 2007, after Schering listed the '274 and '463 patents in

the Orange Book, Sandoz filed ANDA 90-127 with the FDA, seeking to obtain approval to engage in commercial manufacture, use and sale of the Sandoz ANDA Product prior to expiration of the '274 and '463 patents.

21. Because Schering had listed the '274 and '463 patents in the Orange Book for the Schering NDA 21-605 Product, Sandoz was required to and did include in its ANDA 90-127 submission certain certifications with respect to the '274 and '463 patents.

22. In particular, Sandoz certified in its ANDA, among other things, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the claims of the '274 and '463 patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Sandoz ANDA Product. Sandoz's certifications are known as paragraph IV certifications because they were made pursuant to subparagraph IV of 21 U.S.C. § 355(j)(2)(A)(vii).

23. Under 35 U.S.C. § 271(e)(2)(A), Sandoz's submission of its paragraph IV certification to the FDA for each of the '274 and '463 patents, which Schering had listed in the Orange Book, may be considered an "artificial" or "technical" act of infringement for subject matter jurisdiction purposes.

24. On or about February 19, 2008, in accordance with 35 U.S.C. § 355(j)(2)(B)(i) and (ii), Sandoz gave written notice to Schering of Sandoz's filing of ANDA 90-127 with paragraph IV certifications with respect to the '274 and '463 patents ("Sandoz Notice").

25. In the Sandoz Notice, Sandoz provided to Schering, among other things, factual and legal bases relating to Sandoz's paragraph IV certifications as to why the Sandoz ANDA Product does not infringe the '274 and '463 patents.

26. Sandoz also provided to Schering, with the Sandoz Notice, an Offer of Confidential Access pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III) to relevant sections of Sandoz's

ANDA 90-127.

27. On or about April 3, 2008, Schering filed a lawsuit against Sandoz in this Court, alleging infringement of the '274 patent based on Sandoz's submission of ANDA 90-127.

28. Even though Schering had caused the FDA to list the '463 patent in the Orange Book for the Schering NDA 21-605 Product, which meant that Schering believed the '463 patent claims a drug for which Schering submitted the NDA or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug, Schering did not include allegations of infringement of the '463 patent in its complaint against Sandoz.

29. Sandoz brings this counterclaim to obtain a final judgment of noninfringement of the '463 patent, which Schering listed in the Orange Book but did not include in the Complaint against Sandoz.

30. Section 271(e)(5) of title 35 specifically provides that the Court shall have subject matter jurisdiction under section 2201 of title 28 for a declaratory judgment that an unasserted Orange Book patent such as the '463 patent is invalid or not infringed.

31. There is a justiciable case or controversy between Sandoz and Schering with respect to infringement of the '463 patent.

32. The Sandoz ANDA Product has not infringed, is not infringing, and will not infringe any valid or enforceable claim of the '463 patent.

33. Sandoz has not, does not and will not induce or contribute to any infringement of any valid or enforceable claim of the '463 patent with respect to the Sandoz ANDA Product.

PRAYER FOR RELIEF

WHEREFORE, Sandoz seeks judgment against Schering:

A. Dismissing with prejudice all of Schering's claims and denying all Schering's requests for relief;

B. Adjudging that U.S. Patent No. 6,100,274 is not and has not been infringed by the Sandoz ANDA Product;

C. Adjudging that U.S. Patent No. 6,100,274 is invalid;

D. Enjoining Schering and its agents, representatives, attorneys and those persons in active concert or participation with them who receive actual notice hereof from threatening or initiating infringement litigation against Sandoz or its customers, dealers or suppliers, or any prospective or present sellers, dealers, distributors or customers of Sandoz, or charging them either orally or in writing with infringement of U.S. Patent No. 6,100,274;

E. Adjudging that U.S. Patent No. 6,979,463 is not and has not been infringed by the Sandoz ANDA Product;

F. Enjoining Schering and its agents, representatives, attorneys and those persons in active concert or participation with them who receive actual notice hereof from threatening or initiating infringement litigation against Sandoz or its customers, dealers or suppliers, or any prospective or present sellers, dealers, distributors or customers of Sandoz, or charging them either orally or in writing with infringement of U.S. Patent No. 6,979,463;

G. Declaring that this action an exceptional case within the meaning of 35 U.S.C. § 285 and that Sandoz is entitled to recover its reasonable attorneys' fees upon prevailing in this action; and

H. Awarding Sandoz its costs and reasonable attorneys' fees, and such other and further relief as the Court deems just and equitable.

Respectfully submitted,

HILL WALLACK LLP

Attorneys for Defendant Sandoz Inc.

Dated: August 6, 2008

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2 and 40.1

I HEREBY CERTIFY that the matter in controversy is related to another case involving defendant Sandoz Inc. herein, namely Sepracor Inc., et al. v. Sun Pharmaceutical Industries, Inc. et al., 07-4213 (MLC)(TJB) and the cases consolidated therein; and several other matters involving plaintiff and defendant herein and/or other defendants, which have been consolidated into Schering Corporation v. Zydus Pharmaceuticals, USA, Inc. et al., 06-4715 (MLC)(TJB) and In re Desloratadine Patent Litigation, MDL 1851, 07-3930 (MLC)(TJB)

Dated: August 6, 2008

/s/Eric I. Abraham
Eric I. Abraham

CERTIFICATION PURSUANT TO L. CIV. R. 201.1

Pursuant to L. Civ. R. 201.1, the undersigned counsel for Sandoz Inc. hereby certifies that Sandoz Inc.'s causes of action as asserted in its counterclaims seek primarily declaratory judgment relief. This action, therefore, is not appropriate for compulsory arbitration.

Dated: August 6, 2008

/s/Eric I. Abraham
Eric I. Abraham

F.R.C.P. RULE 7.1 DISCLOSURE STATEMENT

ERIC I. ABRAHAM, of full age, under oath, hereby declares as follows:

1. I am a member of the Bar of the State of New Jersey and am admitted to practice before the United States District Court for the District of New Jersey.

2. I represent Defendant Sandoz Inc.

3. Sandoz Inc. is wholly owned by Novartis Pharmaceuticals Corp. of East Hanover, New Jersey.

4. Novartis Pharmaceuticals Corp. is wholly owned by Novartis Corporation of New York, New York.

5. Novartis Corporation is wholly owned by Novartis AG, which is publicly traded under the symbol NVS.

I declare that the foregoing statements made by me are true. I am aware that if any of the foregoing statements made by me are willfully false, I am subject to punishment. Executed on August 6, 2008.

/s/Eric I. Abraham
Eric I. Abraham

CERTIFICATE OF SERVICE

This is to certify that a true and correct copy of the foregoing **ANSWER, DEFENSES, AND COUNTERCLAIMS OF SANDOZ INC. TO SCHERING CORPORATION'S COMPLAINT,** and **CERTIFICATIONS PURSUANT TO L. CIV. R. 11.2, 40.1 and 201.1,** and **F.R.C.P. RULE 7.1 DISCLOSURE STATEMENT** are to be electronically filed. Notice of this filing will be sent to all parties by operation of the Court's electronic filing system. Parties may access this filing through the Court's system.

August 6, 2008
Date

/s/Eric I. Abraham
Eric I. Abraham

EXHIBIT A

US006979463B2

(12) **United States Patent**
Kou

(10) **Patent No.: US 6,979,463 B2**
(45) **Date of Patent: Dec. 27, 2005**

(54) **STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION**

(75) Inventor: **Jim H. Kou**, Basking Ridge, NJ (US)

(73) Assignee: **Schering Corporation**, Kenilworth, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 464 days.

(21) Appl. No.: **10/175,460**

(22) Filed: **Jun. 19, 2002**

(65) **Prior Publication Data**

US 2003/0086971 A1 May 8, 2003

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/US00/34412, filed on Dec. 19, 2000.

(60) Provisional application No. 60/172,836, filed on Dec. 20, 1999.

(51) **Int. Cl.**[7] **A61K 9/20**; A61K 9/28
(52) **U.S. Cl.** **424/464**; 424/474; 424/484
(58) **Field of Search** 424/464, 474, 424/484

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(74) *Attorney, Agent, or Firm*—Thomas D. Hoffman; Robert J. Lipka; Covington & Burling

(57) **ABSTRACT**

A film-coated extended release solid oral dosage composition containing a nasal decongestant, pseudoephedrine or salt thereof, e.g., pseudoephedrine sulfate in a core effective to provide a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hrs to about 8.40 hrs and having two or three film-coatings on the core, the second one containing an amount of the non-sedating antihistamine, desloratadine, effective to provide a geometric maximum plasma concentration of desloratadine of about 2.15 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours, and use of the composition for treating patients showing the signs and symptoms associated with allergic and/or inflammatory conditions of the skin and airway passages are disclosed.

32 Claims, No Drawings

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STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION

BACKGROUND OF THE INVENTION

This invention relates to a film-coated extended release solid oral dosage composition containing a nasal decongestant, e.g., pseudoephedrine in a controlled release core and a film outer coating containing the non-sedating antihistamine, desloratadine. The solid oral dosage compositions of this invention are useful for treating patients showing the signs and symptoms associated with allergic and/or inflammatory conditions such as the common cold, as well as signs and symptoms associated with allergic and/or inflammatory conditions of the skin or upper and lower airway passages such as allergic rhinitis, seasonal allergic rhinitis and nasal congestion. upper respiratory diseases, allergic rhinitis and nasal congestion.

Desloratadine, also called descarbethoxyloratadine, is disclosed in U.S. Pat. No. 4,659,716 as a non-sedating antihistamine useful as an anti-allergy agent. U.S. Pat. No. 6,100,274 discloses compositions containing desloratadine. U.S. Pat. No. 5,595,997 discloses methods and compositions for treating seasonal allergic rhinitis symptoms using desloratadine. Desloratadine, upon oral absorption, is hydroxylated at the 3 position to produce the metabolite, 3-hydroxyldesloratadine.

U.S. Pat. Nos. 4,990,535 and 5,100,675 disclose a twice-a-day sustained release coated tablet wherein the tablet coating comprises descarbethoxyloratadine and a hydrophilic polymer and polyethylene glycol, and the tablet core comprises acetaminophen, pseudoephedrine or a salt thereof, a swellable hydrophilic polymer and pharmaceutically acceptable excipients.

U.S. Pat. No. 5,314,697 discloses an extended release tablet containing matrix core comprising pseudoephedrine sulfate and a coating comprising loratadine.

None of the prior art discloses the once-a-day film-coated solid oral dosage composition of this invention.

The successful development of a formulation of a desloratadine-pseudoephedrine once-a-day product would be desirable, but would require achieving a release rate profile for pseudoephedrine component over an extended period in excess of twelve hours and preferably at least 16 hours while maintaining delivery of an effective once a day dose of desloratadine.

It would be desirable for increased patient compliance to have an extended release desloratadine-pseudoephedrine product effective and safe when used on a once-a-day basis for the treatment, management and/or mitigation of the signs and symptoms associated with the common cold, as well as allergic and/or inflammatory conditions of the skin or upper and lower airway passages such as seasonal, allergic rhinitis and nasal congestion.

SUMMARY OF THE INVENTION

We have discovered a desloratadine-pseudoephedrine once-a-day product which produces a release rate profile for pseudoephedrine over an extended period in excess of twelve hours and preferably at least 16 hours while maintaining delivery of an effective once a day dose of desloratadine.

Thus, the present invention provides film-coated extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a film coating

uniformly covering the core and comprising an effective amount of desloratadine wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hrs to about 8.40 hrs and the amount of desloratadine is effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

More preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours and a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

Thus, in a preferred embodiment, this invention provides a pharmaceutical composition comprising therapeutically effective amount of pseudoephedrine sulfate in a core and an effective amount of desloratadine in a film coating maintaining the desirable pharmacokinetic parameters of desloratadine, 3-hydroxydesloratadine and pseudoephedrine listed herein above.

This invention also provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising about 240 mg of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a film coating uniformly covering the core and comprising about 5 mg of desloratadine wherein total desloratadine degration products in the film-coated extended release oral dosage composition is less than or equal to about 2.0 weight percent. Preferably, total desloratadine degradation products in the film-coated extended release solid oral dosage composition is less than or equal to 1.0 to about 1.5 weight percent, and more preferably is less than or equal to 0.8 to about 1.0 weight percent, after storage of the compositions at 25 C and 60% relative humidity for at least about 24 months.

The major desloratadine degradation products in the film-coated extended release solid oral dosage composition are (1) N-methyl-desloratadine, and (2) N-formyldesloratadine. See Chart.

This invention also provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising about 240 of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a first film coating uniformly covering the core; and (c) a second film coating uniformly covering the first coating comprising about 5 mg of desloratadine; wherein more than about 90% of the desloratadine in solid oral dosage composition dissolves into a stirred 0.1N HCl solution at 37° C. in about 45 minutes, and more than about 90% of the pseudoephedrine sulfate in solid oral dosage composition dissolves into a stirred 0.1N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. over 16 hours.

This invention also provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or phar-

maceutically acceptable salt thereof, and (b) a film coating uniformly covering the core and comprising an effective amount of desloratadine wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric mean steady state maximum plasma concentration of pseudoephedrine of about 382 ng/mL to about 664 ng/mL at a time of about 5.25 hrs to about 7.99 hrs after administration of a daily dose of said composition for at least about 10 consecutive days. and the amount of desloratadine is effective to produce a geometric mean steady state maximum plasma concentration of desloratadine of about about 1.59 ng/mL to about 3.39 ng/mL at a time of about about 2.24 hours to about 5.12 hours after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state maximum plasma concentration of pseudoephedrine is about 418 ng/mL to about 628 ng/mL at a time of about 5.32 hrs to about 7.98 hrs after administration of a daily dose of said composition for at least about 10 consecutive days. and the geometric mean steady state maximum plasma concentration of desloratadine is about about 1.95 ng/mL to about 2.93 ng/mL at a time of about 2.94 hours to about 4.42 hours after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state maximum plasma concentration of 3-hydroxy-desloratadine of about 1.25 ng/mL to about 1.87 ng/mL at a time of about 3.44 hours to about 5.86 hours and a geometric mean steady state value for the area under the plasma concentration-time curve from 0–24 hours for 3-hydroxy-desloratadine was about 20.3 ng hr/mL to about 3.11 ng hr/mL after administration of a daily dose of said composition for at least about 12 consecutive days

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for desloratadine was about 23.0 ng hr/mL to about 46.6 ng hr/mL.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for desloratadine was about 27.8 ng hr/mL to about 41.8 ng hr/mL.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for pseudo-ephedrine was about 6244 ng hr/mL to about 11346 ng hr/mL.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for pseudoephedrine was about 7030 ng hr/mL to about 10554 ng hr/mL.

The present invention also provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a film coating uniformly covering the core and comprising an effective amount of desloratadine, wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric mean steady state minimum plasma concentration of pseudoephedrine of about 82 ng/mL to about 243 ng/mL after administration of a daily dose of said composition for at least about 10 consecutive days and the amount of desloratadine is effective to produce a geometric mean steady state minimum plasma concentration of desloratadine of about 0.307 ng/mL to about 1.095 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state minimum plasma concentration of pseudoephedrine is about 129 ng/mL to about 193 ng/mL after administration of a daily dose of said composition for at least about 10 consecutive days and the geometric mean steady state minimum plasma concentration of desloratadine is about 0.624 ng/mL to about 0.946 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state minimum plasma concentration of 3-hydroxy-desloratadine of about 0.503 ng/mL to about 0.875 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state minimum plasma concentration of 3-hydroxy-desloratadine of about 0.551 ng/mL to about 0.827 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days

We have also discovered that by placing a first coating between film-coating comprising desloratadine and the core comprising a nasal decongestant, e.g., pseudoephedrine salt, preferably pseudoephedrine sulfate, provides release of desloratadine from the second film-coating and extended release of the nasal decongestant pseudoephedrine sulfate from the core, preferably a matrix core, over a period in excess of twelve hours while maintaining the desirable pharmacokinetic parameters of desloratadine, 3-hydroxy-desloratadine and pseudoephedrine listed herein above and wherein the total desloratadine degradation products produced is less than or equal 2.0 weight percent, preferably is less than or equal 1.0 to about 1.5 weight percent, and more preferably is less than or equal to 0.8 to about 1.0 weight percent, after storage of the compositions at 25 C and 60% relative humidity for at least about 24 months.

Thus, in a preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a). a matrix core comprising:
1. an extended release amount of a pharmaceutically acceptable decongestant;
2. a polymer matrix;
3. a water insoluble basic calcium, magnesium or aluminum salt;
4. a binder;
5. a lubricant; and optionally,
6. a glidant;

(b) a first film coating uniformly covering the matrix core comprising;
1. a water-swellable film-forming neutral or cationic copolymeric ester;

2. a lubricant;
3. a film-modifier; and
4. optionally, an anti-foaming agent;

(c) a second film coating uniformly covering the first coating, comprising:
1. an immediate release amount of desloratadine;
2. a water-swellable film-forming neutral or cationic copolymeric ester;
3. a lubricant;
4. a water soluble film-modifier; and optionally,
5. an anti-foaming agent;

The film-coated extended release solid oral dosage compositions of the present invention release at least about 80%, and preferably at least about 90% of the desloratadine into a 0.1N HCl solution at 37° C. within about 45 minutes and at least about 50% of the pseudoephedrine sulfate dissolves into a stirred 0.1N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. in 5 hours. and at least about 80% of the pseudoephedrine sulfate dissolves into the stirred solution in 10 hours and at least about 93% of the pseudoephedrine sulfate dissolves into the stirred solution in 16 hours.

In another preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a) a matrix core comprising:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160–480
Ethylcellulose	about 40–120
Dibasic Calcium Phosphate Dihydrate	about 56–162
Povidone	about 20–60
Silicon Dioxide	about 6–12
Magnesium Stearate	about 2–6
Approximate Matrix Core Weigh Range:	about 518–1082 mg

and

(b) a first film coating uniformly covering the matrix core comprising:
(1) a neutral copolymer of ethyl acrylate and methyl acrylate;
(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;
(3) a polyethylene glycol selected form polyethylene glycol 200 to polyethylene glycol 8000; and
(4) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel; and

(c) a second film coating uniformly coating the first coating, comprising:
(1) an amount of desloratadine effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;
(2) a neutral copolymer of ethyl acrylate and methyl acrylate;
(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;
(4) a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000; and optionally
(5) a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

The above-listed preferred film-coated extended solid oral dosage composition may further comprise a third film coating uniformly covering the second film coating, wherein the third film coating comprises:
(1) a neutral copolymer of ethyl acrylate and methyl acrylate;
(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;
(3) an effective amount of at least one a water-soluble film-modifying agent selected from low viscosity hydroxypropyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose, and a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000 or mixtures thereof;
(4) a pharmaceutically acceptable dye; and
(5) optionally a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

In a more preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a) a matrix core comprising:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160–480
Ethylcellulose	about 40–120
Dibasic Calcium Phosphate Dihydrate	about 54–162
Povidone	about 20–60
Silicon Dioxide	about 6–12
Magnesium Stearate	about 2–6
Approximate (Matrix Core) Weight Range:	about 518–1082 mg

(b) a first film coating uniform by covering the matrix core comprising:

Ingredient	mg/first coating
(d) a neutral copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800,000;	about 1.36–about 4.08
(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;	about 1.36–about 4.08
(3) a polyethylene glycol selected from a polyethylene glycol 6000 to a polyethylene glycol 8000 and	about 0.136–about 0.408
(4) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel;	about 0.11–about 0.33
Total for first film coating: and	about 2.96–8.89 mg

(c) a second film coating uniformly coating the first coating, said second film comprising:

Ingredient	mg/second film coating
(1) a 24-hour amount of desloratadine;	about 5.0–about 6.0
(2) a neutral copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800,000;	about 3.04–about 9.12
(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;	about 3.5–about 10.5

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(4)	a polyethylene glycol selected from a polyethylene glycol 6000 to a polyethylene glycol 8000; and	about 0.915–about 2.75
(5)	optionally, a pharmaceutically acceptable mixture of homologous liquid methyl silsoxane polymers and silica gel;	about 0.14–about 042
	Total for second coating:	about 12.60–about 38.79 mg

In a preferred embodiment, the present invention provides a film-coated extended release oral dosage composition comprising:

(a) a matrix core comprising:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160–480
Ethylcellulose	about 40–120
Dibasic Calcium Phosphate	about 56–162
Povidone	about 20–60
Silicon Dioxide; and	about 6–12
Magnesium Stearate	about 2–6
Approximate Matrix Core Weight Range:	about 518–1082 mg

(b) a first film coating uniform by covering the matrix core comprising:

(1) a neutral copolymer of ethyl acrylate and methyl acrylate having molecular weight of 800,000;

(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(3) a polyethylene glycol selected from a polyethylene glycol 200 to polyethylene glycol 8000; and

(4) optionally a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel; and

(c) a second film coating uniformly covering the first coating comprising:

(1) an amount of desloratadine effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;

(2) a netural copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800, 000;

(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(4) a polyethylene glycol selected from a polyethylene glycol 200 to a-polyethylene 8000; and

(5) optionally a pharmaceutically acceptable mixture of homogous liquid methyl siloxane and polymers and silica gel.

A more preferred composition of the present invention is provided herein below:

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg

1. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrytalc/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg

2. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	6.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	5.88
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Subtotal for second coating	20.08 mg

3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating:	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore and Three Coatings) Weight:	842.97 mg

Another more preferred composition of the present invention is provided herein below:

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg

2. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72

-continued

	Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
	Subtotal for first coating:	5.93 mg
2.	Second Film (Immediate Release) Coating	mg/tablet
	Desloratadine	5.0
	Simethicone	0.28
	Polyethylene glycol 8000	0.61
	Talc NF	5.17
	Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
	Hydroxypropyl Methylcellulose 2910 USP 6 cps	3.05
	Subtotal for second coating:	20.20 mg
3.	Third Film Coating	mg/tablet
	Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
	Talc NF	5.79
	Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
	Polyethylene Glycol 8000 NF	0.42
	Simethicone	0.11
	Spectra Spray Med Blue Dye	3.65
	Subtotal for third coating	16.24 mg
	Approximate Total of Three Coatings Weight:	42.37 mg
	Approximate Tablet (MatrixCore & Three Coatings) Weight:	842.37 mg

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudo-ephedrine hydrogen chloride was used in place of pseudoephedrine sulfate.

The compositions of the present invention are useful for treatment of allergic and/or inflammatory conditions of the skin (e.g. urticaria) and the upper and lower airway passages including the nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion in patients in need of such treating.

DETAILED DESCRIPTION OF THE INVENTION

During the course of development of the compositions of the present invention, desloratadine was found to be unstable and to discolor when stored in combination with various excipients such as those disclosed in U.S. Pat. No. 5,314,697 as part of the matrix core containing pseudoephedrine sulfate. The excipients causing discoloration and instability of desloratadine include acidic excipients having a pH of less than 7 in water such as organic acids, such as stearic acid, povidone, crospovidone and carbonyl-containing materials such as lactose, and ethyl cellulose and hydroxylpropyl methylcellulose. Binders like povidone and polymers such as hydroxypropymethylcellulose are useful as a polymer matrix for the sustained release of the pseudoephedrine sulfate from the inner polymer matrix core.

We discovered that by uniformly covering the inner core matrix containing a nasal decongestant, e.g., pseudoephedrine sulfate and hydroxypropyl methylcellulose, ethyl cellulose and povidone with a first coating comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and lubricant, the desloratadine could safely be coated onto the first coating. The desloratadine was found to have an acceptable immediate release profile from the second coating (about 80%, and preferably at least about 90% of the desloratadine is released in 0.1N HCl in less than about 45 min.) and total desloratadine degradation products in the film-coated extended release solid oral dosage composition is less than or equal to 1.0 to about 1.5 weight percent, and more preferably is less than or equal to 0.8 to about 1.0 weight percent, after storage for at least 24 months at 25° C. and about 60% relative humidity ("RH").

When a third film coating comprising a water swellable film-forming neutral or cationic co-polymeric ester and polyethylene glycol as a film modifier was placed on top of the second coating, the dissolution rate of desloratadine from the second coating and pseudoephedrine from the core decreased to unacceptably low levels.

Surprisingly, addition of a low viscosity hydroxylpropyl methylcellulose to the third coating as a film-modifier, restored the dissolution rates of both active ingredients (pseudoephedrine sulfate and desloratadine) to levels approximately the same as those obtained when a core matrix was uniformly covered with two film coatings.

The phrase "allergic and inflammatory conditions of the skin and airway passages" is meant those allergic and inflammatory conditions and symptoms found on the skin and in the upper and lower airway passages from the nose to the lungs. Typical allergic and inflammatory conditions of the skin and upper and lower airway passages include seasonal and perennial allergic rhinitis, non-allergic rhinitis, asthma including allergic and non-allergic asthma, sinusitis, colds (in combination with a NSAID, e.g., aspirin, ibuprofen or acetaminophen) and/or a decongestant e.g. pseudoephedrine), dermatitis, especially allergic and atopic dermatitis, and urticaria and symptomatic dermographism as well as retinophathy, and small vessel diseases, associated with diabetes mellitus.

The amount of desloratadine effective for treating or preventing allergic and inflammatory conditions of the skin and upper and lower airway passages will vary with the age, sex, body weight and severity of the allergic and inflammatory condition of the patient. Typically, the amount of desloratadine effective for treating or preventing such allergic and inflammatory conditions is in the range of about 2.5 mg/day to about 60 mg/day, preferably about 2.5 mg/day to about 20 mg/day, or about 4.0 mg/day to about 15 mg/day, or about 5.0 mg/day to about 10 mg/day, more preferably about 5.0 mg/day to about 10.0 mg/day, and most preferably about 5.0 mg/day to about 6.0 mg/day in a single dose.

Desloratadine is a non-sedating long acting histamine antagonist with potent selective peripheral H1-receptor antagonist activity. Following oral administration, loratadine is rapidly metabolized to descarboethoxyloratadie or desloratadine, a pharmacologically active metabolite. In vitro and in vivo animal pharmacology studies have been conducted to assess various pharmacodynamic effects of desloratadine and loratadine. In assessing antihistamine activity in mice (comparison of ED_{50} value), desloratadine was relatively free of producing alterations in behavior alterations in behavior, neurologic or autonomic function. The potential for desloratadine or loratadine to occupy brain H1-receptors was assessed in guinea pigs following i.p. administration and results suggest poor access to central histamine receptors for desloratadine or loratadine.

In addition to antihistaminic activity, desloratadine has demonstrated anti-allergic and anti-inflammatory activity from numerous in vitro and in vivo tests. These in vitro tests (mainly conducted on cells of human origin) have shown that desloratadine can inhibit many events in the cascade of allergic inflammation. These anti-inflammatory effects for desloratadine are independent of the H1-antagonist effect of

desloratadine and include: The release of inflammatory mediators histamine, truptase, leukotriene and prostaglandin D2 from mast cells;

The release of inflammatory cytokines including IL-4, IL-6, IL-8 and IL-13; The release of the inflammatory chemokines such as RANTES (regulated upon activation, normal T cell expressed and presumably secreted); Superoxide anion production of polymorphonuclear neutrophils; The expression of cell adhesion molecules such as intracellular adhesion molecules (ICAM-1) and P-selection in endothelial cells; and Eosinophil migration and adhesion. In vivo studies also suggest that an inhibitory effect of desloratadine on allergic bronchospasm and cough can also be expected.

The clinical efficacy and safety of desloratadine has been documented in over 3,200 seasonal allergic rhinitis patients in 4 double-blind, randomized clinical trials The results of these chemical studies demonstrated the efficacy of desloratadine in the treatment of adult and adolescent patients with seasonal rhinitis.

The nasal decongestants useful in the present invention include phenylpropanolamine, phenylephrine and and pseudoephedrine. Pseudoephedrine as well as pharmaceutically acceptable acid additional salts, e.g., those of HCl or H_2SO_4, is a sympathomimetic drug recognized by those skilled in the art as a safe therapeutic agent effective for treating nasal congestion and is commonly administered orally and concomitantly with an antihistamine for treatment of nasal congestion associated with allergic rhinitis. The use of pseudoephedrine as a nasal decongestant in the present invention is preferred; the use of pseudoephedrine sulfate is more preferred.

In the course of development of the oral dosage composition of this invention, it was discovered that the selection of the polymers for the polymer matrix core was critical to achieve the desired extended release period of at least 12 hours, preferably 12 to 16 hours and more preferably for at least 16 hours for pseudoephedrine sulfate. For example, the use of hydroxypropyl methyl cellulose 4,000 cps or 15,000 cps as polymers in the matrix core did not provide this more preferred extended release period of at least 16 hours for dose of pseudoephedrine sulfate. We discovered that only by selecting for inclusion into the matrix core of specific weight ratios of three specific polymers was the desired pseudoephedrine release profile achieved. Only by combining (1) four parts by weight of hydroxypropyl methyl cellulose 2208 USP, 100,000 cps with (2) one part by weight of ethyl cellulose together with (3) ½ part by weight of povidone as a secondary binder was the more preferred extended release profile of at least 16 hours for pseudoephedrine sulfate from the matrix core achieved. The matrix core also contains specific amounts of silicon dioxide as a glidant and magnesium stearate as a lubricant. The tablet hardness 22±6 Strong-Cobb Units (SCU) is not greatly affected by the higher level of lubricant (6 mg/tablet) but it is preferred to maintain the lubricant level at ⅒ part by weight of lubricant to one part by weight of povidone as secondary binder.

The term "lubricant" as used herein refers to a substance added to the dosage form to enable the dosage form, e.g., a tablet, after it has been compressed to releases from the mold or die.

Suitable lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and the like. Preferably, magnesium stearate or talc is used.

The term "glidants" as used herein refers to a substance, such as an anti-caking agent, which improves the flow characteristics of a powder mixture.

Suitable glidants include silicon dioxide and talc. Preferably, silicon dioxide is used.

The term "binders" as used herein means any material that is added to pharmaceutical compositions to help hold such compositions together and release the medicament therefrom.

Suitable binders are selected from the group consisting of: croscarmellose sodium, a cross-linked polymer of carboxymethylcellulose sodium, povidone, crospovidone, starches, celluloses, alginates, and gums; see also USP XXII page 1858 (1990). Preferably, povidone is used.

Typically suitable antifoaming agents include mixtures of homologous liquid methylsiloxane and silica gel available under the Simethecone tradename.

The term "water-swellable film-forming neutral or cationic copolymeric ester," as used herein means neutral and cationic copolymers of ethyl acrylate and substituted unsubstituted methyl or ethyl methacrylate esters.

Typically suitable water swellable film-forming neutral copolymeric esters include neutral copolymers of ethyl acrylate and methyl metharylate such as are available from Pharma Poloymers, a company of the Hüls Group under the EUDRAGIT® Tradename; EUDRAGIT NE30D. and Kollicoat available from BASF, Mt Olive, N.J. An aqueous dispersion containing 30% by weight of a neutral copolymer based on ethyl crylate and methyl methoacrylate (average molecular weight of approximately 800,000) is preferred.

Typically suitable water-swellable film-forming cationic co-polymeric esters include cationic co-polymerers based on dimethylaminoethylmethacrylate and a neutral methacrylic ester such as the EUDRAGIT E copolymers available from Pharma Polymers as a 12.5% solution (EUDRAGIT E 12.5) or as solid (EUDRAGIT E 100) and quaternay ammonium copolymers described in USP/NF as "Amononio methacrylate copolymer, Type A" and Type "B". Such copolymers are available as aqueous dispersions of copolymers of acrylic and methacrylic acid esters with a low (substitution) content of quaternary ammonium groups present as salts, (e.g., quaternary ammonium chlorides). Type A and Type B are available as 30% aqueous dispersions under the EUDRAGIT RL 30D and EUDRAGIT RS 30D tradenames, respectively. Use of the water-swellable film—from neutral co-polymeric esters based on ethyl acrylate and methacrylate is preferred.

The term "water soluble film modifier" as used herein means a film-forming agent which modifies the water-swellable characteristics of the film-forming neutral or cationic copolymeric esters useful in the compositions of the present invention. A typically suitable water soluble film-modifying agent is a low viscosity (≦20 cps) cellulose such as low viscosity hydroxypropyl methyl cellulose, low viscosity hydroxylethyl methyl cellulose; low viscosity sodium carboxymethyl cellulose or a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000.

Use of a polyethylene glycol 6000 to polyethylene glycol 8000 as a film modifier is preferred in the first and second coatings; the use of polyethylene glycol 8000 in each coating is more preferred.

Use of polyethylene glycol in combination with a low viscosity hydroxypropyl methylcellulose in the third coating is preferred. Use of a mixture of polyethylene glycol 8000 and hydroxypropyl methylcellulose 2910 cps in the third or outermost film coating is more preferred.

The term "water insoluble basic calcium, magnesium and aluminium salts" as used herein means the pharmaceutically acceptable carbonates, phosphates, silicates and sulfates of calcium, magnesium and aluminum or mixtures thereof.

Typically suitable pharmaceutically acceptable basic salts include calcium sulfate anhydrous, hydrates of calcium sulfate, such as calcium sulfate dihydrate, magnesium sulfate anhydrous, hydrates of magnesium sulfate, dibasic calcium phosphate, dibasic calcium silicate, magnesium trisilicate, magnesium phosphate, aluminum silicate, and hydrates of magnesium phosphate, aluminum phosphate; and calcium phosphate is more preferred. The use of dibasic calcium phosphate dihydrate is most preferred.

The hydroxylpropyl methylcellulose 2910 acts as a film-forming agent in the film coating, and the polyethylene glycols act as film modifier. Other suitable film-forming polymers which may be used include low viscosity (720 cps) hydroxypropyl celluloses, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose.

The oral dosage composition of this invention also provides a shelf life of more than 24 months, e.g., up to 36 and 48 months so long as the tablets are stored in standard package at between 2° and 30° C. in an ambient environment of 60% relative humidity.

In the preparation of the tablet core, the povidone is dissolved in a mixture of alcohol and water. The pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208 USP, 100,000 cps, ethylcellulose, and dibasic calcium phosphate are blended and granulated with an alcoholic water solution containing povidone. The granulation is milled, and dried to a loss on drying between 0.5 to 2.0%.

The dried granulation is milled and blended with requisite amounts of silicon dioxide and magnesium stearate. The final blend is compressed to produce the inner polymer matrix core composition.

The coatings are normally applied to the inner polymer matrix cores in the following manner:

Cores are charged into a suitable coating pan. A water dispersion of talc, Simethicone, polyethylene glycol 8000 and EUDRAGIT NE30D is applied to the matrix cores as a first coating. These coated matrix cores are then coated with a dispersion of desloratadine, Simethicone, EUDRAGIT NE 30D, polyethylene glycol 8000 NF and talc dispersion. This is followed by an application of third coating containing a dispersion of FD & C Blue No. 2 Aluminum lake containing EDTA as a chelating agent, talc, Simethicone, EUDRAGIT NE30D, containing hydroxy-propyl methylcellulose 2910 cps. and polyethylene glycol 8000 NF. The coated tablets are then branded (with black ink) and packaged in plastic bottles and blisters for storage at a temperature between 2° C. and 30° C. in an ambient environment

During the course of development of the formulations of the present invention, we discovered that the in vitro dissolution studies showed a decrease in both the desloratadine release rate and in desloratadine concentration at increased pH, especially pH values>7.0, compared to those for a 5 mg tablet of desloratadine. The in vivo studies showed the Tmax was greater than 4 hours and that a significant part of the absorptive desloratadine process occurs in the small intestine which has an alkaline pH (pH values>7.0).

We discovered we could increase the release of desloratadine by increasing the level of hydroxypropyl methylcellulose and lowering the levels of the plasticizing agent, e.g., polyethylene glycol 8000, and of the lubricant, e.g., talc, in the second film coating containing desloratadine. See Example 4.

In another preferred embodiment, the effective amount of desloratadine in the second film coating was increased to 6.0 mg and amount of talc was reduced (by about 1.12 mg) to produce an acceptable pharmacokinetic profile. See Example 3 and Table 3.

For the solid oral dosage formulations of the present invention, the geometric mean maximum plasma concentration of pseudoephedrine (PES) is about 345 ng/mL to about 365 ng/mL at a time (Tmax) of about 7.60 hours to about 8.40 hours; the geometric mean maximum plasma concentrate of desloratadine (DL) is about 2.10 ng/mL to about 2.45 ng/mL, preferably 2.15 ng/mL to about 2.35 ng/mL at a time (Tmax), of about 4.0 hours to about 4.5 hours and the geometric mean maximum plasma concentrate of 3-hydroxydesloratadine (3-OH-DL) is about 0.75 ng/mL to about 1.15 ng/mL, preferably about 0.85 ng/mL to about 1.05 ng/mL, and more preferably preferably about 0.88 ng/mL to about 1.02 ng/mL at a time (Tmax) of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition to healthy subjects.

Pharmacokinetic Study No. 1

The pharmacokinetic objective of this study was to determine the bioavailability and bioequivalence of desloratadine (DL), 3-OH DL and pseudoephedrine(PES) from the formulation of Example 2 (5 mg of DL/240 mg of PES) of this application relative to that of a 5 mg of Example 11 of U.S. Pat. No. 6,100,274 (U.S. Pat. No. '274) and an extended-release pseudoephedrine core as references. This study was a Phase I, open-label, single-dose, randomized, three-way crossover study with a seven-day washout period between each treatment. Thirty-six healthy male and female subjects received each of the following treatments in the order assigned by a computer-generated random code:

Treatment A:	One 5 mg DL/240 mg PES tablet of Example 2.
Treatment B:	One DL 5 mg tablet of Example 11 of USP.'274.
Treatment C:	One 240 mg pseudoephedrine sulphate (oval extended-release pseudoephedrine cores from Claritin ® D-24 coated with placebo Claritin ® D-24 coat).

The tablets were administered with 180 mL (6 fluid ounces) of non-carbonated room temperature water. The tablet was swallowed whole, not chewed or crushed. After dosing, the oral cavity was inspected to assure that the subject had swallowed the tablet. Subjects continued fasting until the four-hour study procedures were complete. Water was permitted throughout the fasting period, except for two hours post-dose. The subjects remained awake and seated upright/ambulatory for four hours post-dose. All subjects were confined to the study site until the 120-hour blood samples, vital signs and laboratory tests were obtained.

Serial blood samples (10 mL) were to be collected into tubes containing heparin as an anticoagulant at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 48, 72, 96 and 120 hours post-dose. No food was allowed for four hours after dosing. Drinking water was not allowed from one hour pre-dose to one hour postdose, except for the 120 mL administered with the treatment. Plasma concentrations of pseudoephedrine were determined using a validated liquid chromatography with tandem mass spectrometric (LC/MS/MS) method with a lower limit of quantitation (LOQ) of 10.0 ng/mL, and a linear range of 10.0–400 ng/mL. The associated mean pharmacokinetic parameters are provided in Table 1.

The mean DL Cmax following administration of DL tablet of Example 2 of the present invention or a 5 mg desloratadine tablet of Example 11 of U.S. Pat. No. 6,100,274 were 1.79 and 2.23 ng/mL, respectively, and were reached at mean Tmax values of 6.78 and 5.10 hours, respectively.

TABLE 1

Mean (% CV[a]) Pharmacokinetic Parameters of DL, and 3-OH DL in Healthy Subjects Following Single-Dose Oral Administration of DL D-24 and DL

	DL			
	Example 2- 5 mg/240 mg (Treatment A)		Example 11 of USP'274-5 mg (Treatment B)	
Parameter (units)	Mean	% CV	Mean	% CV
Cmax (ng/mL)	1.79	35.8	2.23	34.8
Tmax (hr)	6.78	57.3	5.10	52.5
	3-OH DL			
	Example 2- D-24 5 mg/240 mg (Treatment A)		Example 11 of USP'274-5 mg (Treatment B)	
Parameter (units)	Mean	% CV	Mean	% CV
Cmax (ng/mL)	0.695	59.4	0.832	55.2
Tmax (hr)	6.09[b]	32.7	4.96[b]	31.4

[a]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.
[b]n = 35

The mean 3-OH DL Cmax following administration of 5 mgDL/240 mgPES tablet of Example 2 of this application and a 5 mg desloratadine tablet of Example 11 of U.S. Pat. No. 6,100,274 were 0.695 and 0.832 ng/mL, respectively, and were reached at mean Tmax values of 6.09 and 4.96 hours, respectively. The peak plasma concentration of 3-OH DL decreased slowly with half-life of 29.6 hours following administration of 5 mgDL/240 mgPES tablet of Example 2 of this application, and 29.5 hours following administration of the 5 mg DL tablet of U.S. Pat. No. 6,100,274.

Statistical comparisons of Cmax and AUC(tf) following administration of tablet of Example 2 of this application and 5 mg desloratadine tablet of U.S. Pat. No. 6,100,274 were performed for DK and 3-OH DL plasma concentrations.

The results showed that the 90% confidence intervals for DL and 3-OH DL did not meet the 80–125% bioequivalence guidelines for both Cmax and AUC(tf). For those subjects where AUC(I) could be determined, the confidence intervals of DL for AUC(I) did not meet the 80–125 bioequivancy guidelines. However, the confidence intervals of 3-OH DL for AUC(I) did meet the 80–125 bioequivances guidelines.

The mean pharmacokinetic parameters of pseudoephedrine are provided in Table 2.

TABLE 2

Mean (% CV[a]) Pharmacokinetic Parameters of Pseudoephedrine in Healthy Subjects Following Single-Dose Oral Administration of DL D-24 and 240 mg Pseudoephedrine Sulphate (Oval Extended-Release Pseudoephedrine Cores from Claritin ® D-24 Coated with Placebo Claritin ® D-24 Coat) Tablets (n = 36)

	Pseudoephedrine			
	5 mg/240 mg Tablet of Example 2 of this application		Pseudoephedrine Sulphate (Oval-Extended Release Pseudoephedrine Cores from Claritin D-24)	
	Mean	% CV	Mean	% CV
Cmax (ng/mL)	328	25	349	18.1
Tmax (hr)	8.42	34	7.36	36.3
AUC (tf) (ng-hr/mL)	6438	42	6225	38.5
tf (hr)	44.0	37	40.0	25.8
AUC (I) (ng-hr/mL)	6780	40	6452	37.3
t½ (hr)	10.3	148	7.25	21.6

[a]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

The mean pseudoephedriine Cmax following administration of the (5 mg DL/240 mgPES) tablet of Example 2 or a 240 mg pseudoephedrine sulphate extended-release core were 328 and 349 ng/mL, respectively. Statistical comparisons of Cmax and AUC(tf) values for DL D-24 (5 mg/240 mg) versus 240 mg pseudoephedrine sulphate (extended-release core) were performed. The power to detect a 20% difference in treatment means at an α-level of 0.05 (two-tailed) for the log-transformed Cmax and AUC(tf) were 100 and 93%, respectively.

The 90% confidence intervals for pseudoephedrine met the 80–125% bioequivalence guidelines for both Cmax and AUC(tf). For those subjects were AUC(I) could be determined, the confidence intervals for AUC(I) also met the 80–125 guidelines.

Pharmacokinetic Study No. 2

Subjects were confined at the study site at least 12 hours prior to each treatment (Day—1). In the morning of Day 1, following a ten-hour overnight fast, each subject received one of the following treatments based on his/her subject number and the study period:

Treatment A: One (5 mg DL/240 mgPES) tablet of Example 2 of this application

Treatment B: One (6 mgDL/240 mgPES) tablet of Example 3 of this application

Treatment C: One 5 mg DL tablet of Example 11 of U.S. Pat. No. '274 plus one 120 mg PES tablet (oval extended-release pseudoephedrine core)

The study procedures, blood collection times and the analytical methodologies summarized in Study No. 1 were employed.

The mean pharmacokinetic parameters are shown in Table 3. The power to detect a 20% difference in treatment means of DL at an α-level of 0.05 (two tailed) for the log-transformed AUC(tf), AUC(I), and Cmax values were 89%, 90% and 88% respectively.

TABLE 3

Mean (% CV[1]) Pharmacokinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Adult Volunteers (n = 42) Following Single-Dose Oral Administration of DI Tablets of Examples 2 (5 mg DL/240 mgPES), Example 3 (6 mg DL/240 mg PES) or a 5 mg DL Tablet of USP'274 Plus One 240 mg PES Tablet.

Treatment	Cmax (ng/mL)	% CV	Tmax (hr)/	% CV
	DL			
A[2]	1.91	44	4.69	52
B[3]	2.35	43	4.33	50
C[4]	2.28	40	3.87	67
	3-OH DL			
A[2]	0.77	28	6.67	52
B[3]	1.00	39	6.12	48
C[4]	0.93	31	5.68	58
	Pseudoephedrine			
A[2]	353	30	7.71	45
B[3]	362	28	8.14	46
C[4]	349	22	8.31	47

[1]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.
[2]Treatment A = One (5 mg/240 mg) tablet of Example 2.
[3]Treatment B = One (6 mg/240 mg) tablet of Example 3.
[4]Treatment C = One 5 mg DL tablet of Example II of USP 6,100,274 plus one 240 mg pseudoephedrine tablet.

The results show that, based on plasma 3-OH DL concentrations, the (5 mg/240 mg) of Example 2 is not equivalent to the 5 mg DL tablet of Example 11 of U.S. Pat. No. '274 and that the 6 mgDL/240 PESmg of Example 3 and 5 mg DL tablet of Example II of U.S. Pat. No. ',274 are bioequivalent.

The results show that, the bioequivalence of pseudoephedrine from the formulations of Examples 2 & 3 was established relative to the reference product.

Pharmacokinetic Study No. 3

Forty health volunteers were enrolled in this open label, randomized, three-way cross-over, single-dose study. The subjects were randomized to receive, following a ten hour over-night fast:

Treatment A:	5 mg DL/240 mg PES of Example 4 of this appln
Treatment B:	DL 5 mg of Example 11 of USP '274 Plus 240 mg PES

The procedures of Study No. 1 were followed using the above-listed treatments.

The mean pharmacokinetic parameters for DL, 3-OH DL and pseudoephedrine are provided in Table 4.

TABLE 4

Mean (% CV[1]) Pharmacokiinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Adult Volunteers (n = 40) Following Single-Dose Oral Administration of One 5 mg D-24 Tablet of Example 4 or One 5 mg DL Tablet of USP'274 Plus One 240 mg Pseudoephedrine Sulfate Tablet

Treatment	Cmax (ng/mL)	% CV	Tmax (hr)	% CV
	DL			
A[2]	2.15	41	4.13	66

TABLE 4-continued

Mean (% CV[1]) Pharmacokiinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Adult Volunteers (n = 40) Following Single-Dose Oral Administration of One 5 mg D-24 Tablet of Example 4 or One 5 mg DL Tablet of USP'274 Plus One 240 mg Pseudoephedrine Sulfate Tablet

Treatment	Cmax (ng/mL)	% CV	Tmax (hr)	% CV
B[3]	2.30	44	4.83	62
	3-OH DL			
A[2]	0.89	48	5.60	42
B[2]	1.07	36	6.10	37
	Pseudoephedrine			
A[2]	382	34	7.83	29
B[2]	399	32	8.43	36

[1]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.
[2]Treatment A = One (5 mgDL/240 mgPES) tablet of Example 4 of application.
[3]Treatment B = One 5 mg DL tablet of Example 11 of USP 6,100,274 plus one 240 mg pseudoephedrine tablet.

Pharmacokinetic Study No. 4

The pharmacokinetic objective of this study was to determine the pharmacokinetic profile of desloratadine (DL), 3-OH DL and pseudoephedrine(PES) following daily administration of the formulation of Example 5 (5 mg of DL/240 mg of PES) of this application for 14 consecutive days This study was a Phase I, open-label, multiple-dose study for 14 consecutive days. Eighteen healthy male and female subjects were enrolled and 17 completed the study; one discontinued. One 5 mg DL/240 mg PES tablet of Example 5. Was administered in the morning (approximately 8 AM)

The tablets were administered with 180 mL (6 fluid ounces) of non-carbonated room temperature water. The tablet was swallowed whole, not chewed or crushed. After dosing, the oral cavity was inspected to assure that the subject had swallowed the tablet. Subjects continued fasting until the four-hour study procedures were complete. Water was permitted throughout the fasting period, except for two hours post-dose. The subjects remained awake and seated upright/ambulatory for four hours post-dose. All subjects were confined to the study site until the 120-hour blood samples, vital signs and laboratory tests were obtained.

Serial blood samples (10 mL) were to be collected into tubes containing heparin as an anticoagulant at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 48, 72, 96 and 120 hours post-dose. No food was allowed for four hours after dosing. Drinking water was not allowed from one hour pre-dose to one hour postdose, except for the 120 mL administered with the treatment. Plasma concentrations of DL, 3-OH DL and pseudoephedrine were determined using a validated liquid chromatography with tandem mass spectrometric (LC/MS/MS) method with a lower limit of quantitation (LOQ) of 0.025 ng/mL, 0.025 ng/mL, and 10.0 ng/mL, respectively. The The methods were validated over concentration range of 0.025 ng/mL—10.0–400 ng/mL for DL, 0.025 ng/mL—10.0–400 ng/mL for 3-OH DL, and 10.0–400 ng/mL for pseudoephedrine. The associated mean steady state pharmacokinetic parameters are provided in Tables 5 & 6.

TABLE 5

Mean (% CV[a]) Steady State Pharmacokinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Subjects Following Multiple-Dose Oral Administration of DL D-24 For 14 Consecutive Days

	Cmax(ng/mL)		Tmax(hr)		Cavg(ng/mL)		AUC(0–24 h) (ng-hr/mL)	
	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
DL	2.44	35	3.68	39	1.45	34	34.8	34
3-OH DL	1.56	20	4.65	26	1.07	21	25.7	21
Pseudoephedrine	523	27	6.65	21	366	29	8795	29

[a]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.
[b]n = 17

The mean steady state DL Cmax following daily administration of DL tablet of Example 5 of the present invention for 14 consecutive days was 2.44 ng/mL, and was reached at mean Tmax value of 3.68 hours. The mean steady state DL Cavg following administration of tablet was 1.45 ng/mL. The mean steady state AUC(0–24 h) following administration of the tablet was 34.8 ng.hr/mL.. The mean 3-OH DL Cmax following administration of 5 mgDL/240 mgPES tablet of Example 5 of this application was 1.56 ng/mL, and was reached at mean Tmax value 4.65 hour. The mean steady state 3-OH DL Cavg was 1.07 ng/mL. The mean steady state AUC(0–24 h) following administration of the tablet was 25.7 ng.hr/mL.

For the solid oral dosage formulations of the present invention, the geometric mean maximum plasma concentration of pseudoephedrine (PES) is about 382 ng/mL to about 664 ng/mL at a time (Tmax) of about 5.25 hours to about 7.99 hours; preferably, about 418 ng/mL to about 628 ng/mL at a time (Tmax) of about 5.32 hours to about 7.98, and a geometric mean steady state value for the area under the plasma concentration-time curve from 0–24 hours for pseudoephedrine was about 6244 ng hr/mL to about 11346 ng hr/mL, preferably, was about 7030 ng hr/mL to about 10554 ng/mL, after administration of a multiple dose of said composition to healthy subjects for at least 10 consecutive days (steady state attained after 10, days data measured over the 14 days), and the geometric mean maximum plasma concentrate of desloratadine (DL) is about 1.59 ng/mL to about 3.39 ng/mL at a time (Tmax) of about 2.24 hours to about 5.12, preferably, 1.95 ng/mL to about 2.93 ng/mL at a time (Tmax), of about 2.94 hours to about 4.42 hours, and a geometric mean steady state value for the area under the plasma concentration-time curve from 0–24 hours for desloratadine was about 23.0 ng hr/mL to about 46.6 ng hr/mL, preferably, was about 27.8 ng hr/mL to about 41.8 ng hr/mL,after administration of a multiple dose of said composition to healthy subjects for at least 12 consecutive days (steady state attained after 12 days data measured over the 14 days), and the geometric mean maximum plasma concentrate of 3-hydroxydesloratadine (3-OH-DL) is about 1.25 ng/mL to about 1.87 ng/mL at a time (Tmax) of about 3.44 hours to about 5.86 hours, and a geometric mean steady state value for the area under the plasma concentration-time curve from 0–24 hours for 3-hydroxy-desloratadine was about 20.3 ng hr/mL to about 3.11 ng hr/mL after administration of a multiple dose of said composition to healthy subjects for at least 12 consecutive days (steady state attained after 12 days, data measured over the 14 days).

The mean trough concentrations of DL, 3-OH DL, and of pseudoephedrine are provided in Table 6.

TABLE 6

Mean (% CV[a]) Pharmacokinetic Parameters of Pseudoephedrine in Healthy Subjects Following Multiple-Dose Oral Administration of DL D-24 (n = 17) For 14 Consecutive Days

	Cmin (ng/ml)		Percent Fluctuation	
	Mean	% CV	Mean	% CV
DL)	0.788	39	115	14
3-OH DL	0.689	27	82.9	18
Pseudoephedrine	161	51	102	22

[a]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

The steady state conditions for DL and 3-OH DL were attained on Day 12 following daily administration of DL as indicated by a lack of a statistically significant difference ($p>0.301$) in the mean trough plasma concentrations of DL between mean trough plasma concentration of DL Day and that on Day 14. The steady state mean trough plasma concentration for pseudoephedrine was attained on Day 10.

For the solid oral dosage formulations of the present invention, the geometric mean minimum plasma concentration of pseudoephedrine (PES) is about 82 ng/mL to about 243 ng/mL, and preferably, about 129 ng/mL to about 193 ng/mL after administration of a multiple dose of said composition to healthy subjects for at least 10 consecutive days (steady state attained after 10 days,data measured over the 14 days), and the geometric mean minimum plasma concentrate of desloratadine (DL) is about 0.307 ng/mL to about 1.095 ng/mL, preferably, 0.624 ng/mL to about 0.946 ng/mL, after administration of a multiple dose of said composition to healthy subjects for at least 12 consecutive days (steady state attained after 12 days, data measured over the 14 days), and the geometric mean minimum plasma concentrate of 3-hydroxydesloratadine (3-OH-DL) is about 0.503 ng/mL to about 0.875 ng/mL, and preferably about 0.551 ng/mL to about 0.827 ng/mL after administration of a multiple dose of said composition to healthy subjects for at least 12 consecutive days (steady state attained after 12 days, data measured over the 14 days).

EXAMPLE 1

This example illustrates preparation of the preferred oral dosage composition of this invention. The ingredients and specific amounts thereof are listed below.

1. Matrix Core

A. Method of Manufacture:

1. Dissolve povidone in a mixture of 3 parts of alcohol and 1 part of purified water.
2. Combine the pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208, ethylcellulose and dibasic calcium phosphate, dihydrate in a suitable mixing bowl and blend under a nitrogen overlay.
3. Granulate the blend from Step 2 with the solution from Step. 1. pass the wet granulation through suitable milling equipment to breakup large lumps.
4. Dry the wet granulation at about 70° C. in a suitable fluid bed processor to a loss on drying between 0.5 to 2.0% as determined by a moisture balance or equivalent.
5. Pass the dried granules through suitable milling equipment.
6. Add the requisite amounts of silicon dioxide and magnesium stearate to the dried, milled granules and blend.
7. Compress the blend on a suitable tablet press.

The matrix cores are coated in the following manners:

A. Preparation of Coating Dispersions and Solutions

1. First Film Coating Solution

(1) Disperse Simethicone and polyethylene glycol 8000 in a portion of purified water and agitate until completely dissolved.

(2) To the product of step 1, add the remainder of the purified water and the talc; stir the so-formed suspension at room temperature until homogeneous.

(3) Slowly add the so-formed homogeneous suspension of step 2 to the stirred EUDRAGIT NE30D dispersion and continue to mix the so-formed mixture until a homogeneous dispersion is formed. Pass the dispersion through a screen.

(4) Spray the dispersion onto the matrix cores maintained at 40° C.±5° C. on a rotating pan.

(5) Dry the cooled matrix cores on the rotating pan.

2. Second Film Coating Dispersion

(1) Disperse the Simethicone and polyethylene glycol 8000 in a portion of purified water. Add additional water and stir the dispersion at room temperature until completely dissolved.

(2) Slowly add desloratadine to the dispersion of step 1 and mix until a uniform dispersion is formed. Combine with the talc with the so-formed uniform dispersion, and continue agitation until a homogenous suspension is formed.

(3) Add dispersion of step 2 to the EUDRAGIT NE 30D dispersion and mix until a uniform dispersion is formed. Pass the dispersion through a screen.

(4) Spray the requisite amount of the dispersion from step 3 onto the matrix core with the first coating in a rotating pan at 25–27° C.

(5) Dry the coated matrix cores on the rotating pan.

3. The Third Film Coating Solution

(1) Add the hydroypropyl methylcellulose 2910 to hot purified water (75° C.) and agitate until a solution forms. Cool the so-formed solution to room temperature.

(2) To a separate container, add Simethicone and polyethylene glycol 8000 to purified water and continue to mix until a solution is formed.

(3) Add talc to solution of step 2 and continue to mix until a uniform dispersion is formed.

(4) Add the solution of step 1 to the dispersion of step 3 and continue to mix until

(5) Add FD&C Blue No. 2 aluminum lake containing EDTA as a chelating agent to purified water in a third container and

(6) Add the Blue lake solution of step 5 to the dispersion of step 4 and mix until a homogeneous mixture is formed.

(7) Slowly add the mixture of step 6 to a dispersion of EUDRAG IT NE30D and continue to mix until homogeneous.

(8) Pass dispersion of step 6 through 60 mesh screen.

(9) Spray the requisite amount of the dispersion of step 8 onto the twice-coated matrix cores in a rotating pan at 35°–45° C. Dry the thrice-coated matrix cores in the form of tablets in rotating pan.

(10) Remove the so-formed tablets from pan and further dry at 40° for 16 hours.

EXAMPLE 2

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg

2. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg

3. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	7.00
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Subtotal for second coating	20.20 mg

-continued

4. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating:	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore & Three Coatings) Weight:	842.97 mg

The in vitro dissolution profile of the tablet of Example 1 was measured in a stirred 0.1N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. The 80% of desloratadine in the coating was dissolved within the first 45 minutes and the total dose of pseudoephedrine sulfate in the matrix core was slowly released via erosion and dissolution mechanisms over a period of at least 16 hours.

EXAMPLE 3

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg
2. Matrix Core Coatings	
1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg
Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	6.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	5.88
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Subtotal for second coating	20.08 mg
3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	16.24
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore and Three Coatings) Weight:	842.97 mg

EXAMPLE 4

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg
2. Matrix Core Coatings	
1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg
2. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	0.61
Talc NF	5.17
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Hydroxypropyl Methylcellulose 2910 USP 6 cps	3.05
Subtotal for second coating	20.20 mg
3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore and Three Coatings) Weight:	842.37 mg

EXAMPLE 5

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1. The formulation of Example 4 was used except in the second film desloratadine layer the amount of polyethylene glycol 8000 was increased to 1.83 mg and the amount of talc was increased to 7.00 and no HPMC 2910 USP 6 cps was added.

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg

Matrix Core Coatings 2. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrytalc/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg

2. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	7.00
Ethyl Acrylate/Methyl methacrylate neutral copolymer (30% dispersion in water)	6.09
Subtotal for second coating	20.20 mg

3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer (30% dispersion in water)	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore and Three Coatings) Weight:	842.37 mg

The total desloratadine degradation products in the film-coated extended release solid oral dosage composition of Example 5 was 0.8 weight percent after storage of the compositions at 25 C and 60% relative humidity for at least about 24 months. The major desloratadine degradation products are (1) N-methyl-desloratadine which was present at a level of about 0.3 weight percent, and (2) N-formyldesloratadine which was present at a level of about 0.4 weight percent.

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudoephedrine hydrogen chloride was used in place of pseudoephedrine sulfate.

The compositions of the present invention are useful for treatment of allergic and/or inflammatory conditions of the skin (e.g. urticaria) and the upper and lower airway passages including the nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion in patients in need of such treating. The precise dosage and dosage regimen may be varied by the attending clinician in view of the teachings herein depending upon the requirements of the patient, e.g., the patient's age, sex and the severity of the allergic and/or inflammatory condition being treated. Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.

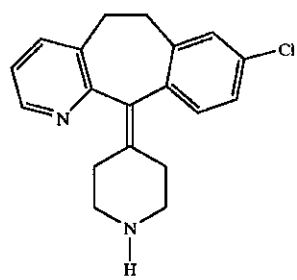
While we have hereinabove presented a number of preferred embodiments of this invention by way of example, it is apparent that the scope of the invention is to be defined by the scope of the appended claims.

The in vitro dissolution profile of the tablets of Examples 1–5 were measured in a stirred 0.1N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. For Example 5, The 91% of desloratadine in the immediate release layer was dissolved within the first 30 minutes, 94% in 45 minutes and 95% of desloratadine was dissolved within 1 hr and the 92–95% of the pseudoephedrine sulfate in the sustained release layer was slowly released via erosion and dissolution mechanisms over a period of at least 16 hours (with 20% in 1 hr, 33% in 2 hrs. and 71% in 8 hrs, 79% in 10 hrs, and 92–95% in 16 hrs).

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudoephedrine hydrochloride was used in place of pseudoephedrine sulfate.

CHART

I



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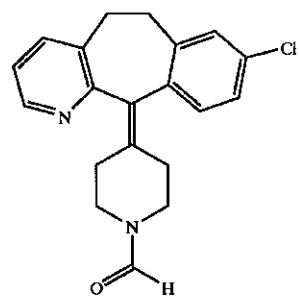

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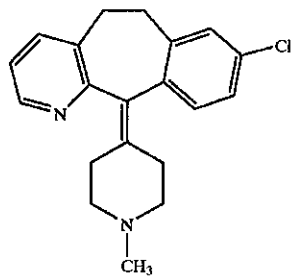
III



What is claimed is:

1. An extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, (b) a first coating covering the core and comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and a lubricant, and (c) a second coating covering the first coating and comprising an effective amount of desloratadine, wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hours to about 8.40 hrs, and the amount of desloratadine is effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition.

2. The extended release solid oral dosage composition of claim 1 wherein the amount of desloratadine is effective to produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

3. The extended release solid oral dosage composition of claim 1 wherein the core is a matrix core and wherein the first coating uniformly covers the matrix core and the second coating uniformly covers the first coating.

4. The extended release solid oral dosage composition of claim 3 wherein (a) the first coating comprises

(1) a water-swellable film-forming neutral or cationic co-polymeric ester;

(2) a lubricant;

(3) a film-modifier; and

(4) optionally, an anti-foaming agent;

and wherein (b) the second coating comprises:

(1) an effective amount of desloratadine sufficient to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;

(2) a water-swellable film-forming neutral or cationic co-polymeric ester;

(3) a lubricant;

(4) a water soluble film-modifier; and

(5) optionally, an anti-foaming agent.

5. The extended release solid oral dosage composition of claim 4 wherein the amount of desloratadine is effective to produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

6. The extended release solid oral dosage composition of claim 4 which further comprises a third coating covering the second coating, said third coating comprising:

(1) a pharmaceutically acceptable dye;

(2) a water-swellable film-forming neutral or cationic copolymeric ester;

(3) a lubricant;

(4) at least one water soluble film-modifier; and

(5) optionally, an anti-foaming agent.

7. The extended release solid oral dosage composition of claim 6 wherein the water-soluble film-modifier is a low viscosity hydroxypropyl methylcellulose, hydroxyethyl methyl cellulose or sodium carboxymethyl cellulose or a polyethylene glycol selected from polyethylene glycol 200 to a polyethylene glycol 8000, or mixtures thereof.

8. The extended release solid oral dosage composition of claim 4 wherein the matrix core comprises a water-insoluble calcium, magnesium or aluminum salt, wherein the water-insoluble calcium, magnesium or aluminum salt is a carbonate, phosphate, silicate or sulfate of calcium, magnesium or aluminum or mixtures thereof.

9. An extended release solid oral dosage composition comprising (a) a core comprising about 240 mg of pseudoephedrine or pharmaceutically acceptable salt thereof, (b) a first coating covering the core and comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and a lubricant, and (c) a second coating covering the first coating and comprising about 5 mg of desloratadine wherein total desloratadine degradation products in the extended release oral dosage composition is less than or equal to about 2.0% by weight.

10. The extended release solid oral dosage composition of claim 9 wherein the total desloratadine degradation products comprise less than or about 0.3 to about 0.4% by weight of N-methyldesloratadine, and less than or about 0.4 to about 0.5% by weight of N-formyldesloratadine.

11. The extended release solid oral dosage composition of claim 9 wherein total desloratadine degradation products in the extended release oral dosage composition comprise less than or about 0.8 to about 1.0 weight percent of the composition.

12. The extended release solid oral dosage composition of claim 9 wherein total pseudoephedrine degradation products in the extended release oral dosage composition comprise less than about 0.5 weight percent to no more than about 1.1 weight percent of the composition.

13. The extended release oral dosage composition of claim 1 wherein the matrix core comprises:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 120 to about 360
Hydroxypropyl Methylcellulose 2208, 100,000 cps	about 160 to about 480
Ethylcellulose	about 40 to about 120
Dibasic Calcium Phosphate Dihydrate	about 56 to about 162
Povidone	about 20 to about 60
Silicon Dioxide	about 6 to about 12
Magnesium Stearate	about 2 to about 6.

14. The extended release oral dosage composition of claim 4 wherein the first film coating comprises:

(1) a neutral copolymer of ethyl acrylate and methyl acrylate;

(2) a lubricant selected from talc, silicon, polyethylene glycol 200 to polyethylene glycol 8000;
(3) a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000; and
(4) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

15. The extended release oral dosage composition of claim **4** wherein the second film coating comprises:
(1) an amount of desloratadine effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;
(2) a neutral copolymer of ethyl acrylate and methyl acrylate;
(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;
(4) a polyethylene glycol selected from polyethylene glycol 200 to a polyethylene glycol 8000; and
(5) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

16. The extended release oral dosage composition of claim **6** wherein the third coating comprises:
(1) a neutral copolymer of ethyl acrylate and methyl acrylate;
(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;
(3) an effective amount of a water-soluble film-modifying agent is a low viscosity hydroxypropyl methylcellulose, hydroxyethyl methylcellulose or sodium carboxymethyl cellulose, or a polyethylene glycol selected from polyethylene glycol 200 to a polyethylene glycol 8000, or mixtures thereof;
(4) a pharmaceutically acceptable dye; and
(5) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

17. An extended release solid oral dosage composition comprising (a) a core comprising about 240 mg of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a first coating comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and a lubricant covering the core; and (c) a second coating covering the first coating comprising about 5 mg of desloratadine; wherein more than about 90% of the desloratadine in solid oral dosage composition dissolves into a stirred 0.1N HCl solution at 37° C. in about 45 minutes, and more than about 90% of the pseudoephedrine sulfate in solid oral dosage composition dissolves into a stirred 0.1 N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. over 16 hours.

18. An extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, (b) a first coating covering the core and comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and a lubricant, and (c) a second coating covering the first coating and comprising an effective amount of desloratadine wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric mean steady state maximum plasma concentration of pseudoephedrine of about 382 ng/mL to about 664 ng/mL at a time of about 5.25 hrs to about 7.99 hrs after administration of a daily dose of said composition for at least about 10 consecutive days and the amount of desloratadine is effective to produce a geometric mean steady state maximum plasma concentration of desloratadine of about 1.59 ng/mL to about 3.39 ng/mL at a time of about 2.24 hours to about 5.12 hours after administration of a daily dose of said composition for at least about 12 consecutive days.

19. The extended release solid oral dosage composition of claim **18** wherein the geometric mean steady state maximum plasma concentration of pseudoephedrine is about 418 ng/mL to about 628 ng/mL at a time of about 5.32 hrs to about 7.98 hrs after administration of a daily dose of said composition for at least about 10 consecutive days and the geometric mean steady state maximum plasma concentration of desloratadine is about 1.95 ng/mL to about 2.93 ng/mL at a time of about 2.94 hours to about 4.42 hours after administration of a daily dose of said composition for at least about 12 consecutive days.

20. The extended release solid oral dosage composition of claim **18** wherein the amount of desloratadine is effective to produce a geometric mean steady state maximum plasma concentration of 3-hydroxy-desloratadine of about 1.25 ng/mL to about 1.87 ng/mL at a time of about 3.44 hours to about 5.86 hours and a geometric mean steady state value for the area under the plasma concentration-time curve from 0–24 hours for 3-hydroxy-desloratadine was about 20.3 ng hr/mL to about 3.11 ng hr/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

21. The extended release solid oral dosage composition of claim **18** wherein the geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for desloratadine was about 23.0 ng hr/mL to about 46.6 ng hr/mL.

22. The extended release solid oral dosage composition of claim **18** wherein the geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for desloratadine was about 27.8 ng hr/mL to about 41.8 ng hr/mL.

23. The extended release solid oral dosage composition of claim **18** wherein the geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for pseudoephedrine was about 6244 ng hr/mL to about 11346 ng hr/mL.

24. The extended release solid oral dosage composition of claim **18** wherein the geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for psudoephedrine was about 7030 ng hr/mL to about 10554 ng hr/mL.

25. An extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, (b) a first coating covering the core and comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and a lubricant, and (c) a second coating covering the the first coating and comprising an effective amount of desloratadine, wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric mean steady state minimum plasma concentration of pseudoephedrine of about 82 ng/mL to about 243 ng/mL after administration of a daily dose of said composition for at least about 10 consecutive days and the amount of desloratadine is effective to produce a geometric mean steady state minimum plasma concentration of desloratadine of about 0.307 ng/mL to about 1.095 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

26. The extended release solid oral dosage composition of claim 25 wherein the geometric mean steady state minimum plasma concentration of pseudoephedrine is about 129 ng/mL to about 193 ng/mL after administration of a daily dose of said composition for at least about 10 consecutive days and the geometric mean steady state minimum plasma concentration of desloratadine is about 0.624 ng/mL to about 0.946 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

27. The extended release solid oral dosage composition of claim 25 wherein the amount of desloratadine is effective to produce a geometric mean steady state minimum plasma concentration of 3-hydroxy-desloratadine of about 0.503 ng/mL to about 0.875 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

28. The extended release solid oral dosage composition of claim 25 wherein the amount of desloratadine is effective to produce a geometric mean steady state minimum plasma concentration of 3-hydroxy-desloratadine of about 0.551 ng/mL to about 0.827 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

29. A method of treating allergic and inflammatory conditions of the upper and lower airway passages and skin which comprises administering to a patient in need of such treatment an effective amount of the extended release solid composition of claim 1.

30. A method of treating nasal congestion associated with allergic and inflammatory conditions of the upper and lower airway passages and skin which comprises administering to a patient in need of such treatment an effective amount of the extended release solid composition of claim 1.

31. A method of treating urticaria which comprises administering to a patient in need of such treatment an effective amount of the extended release solid composition of claim 1.

32. A method of treating the nasal and non-nasal symptoms of perennial and seasonal allergic rhinitis which comprises administering to a patient in need of such treatment an effective amount of the extended release solid composition of claim 1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

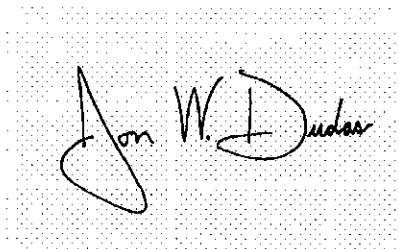
PATENT NO. : 6,979,463 B2
DATED : December 27, 2005
INVENTOR(S) : Kou, Jim H.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 30,
Line 48, replace "psudoephedrine" with -- pseudoephedrine --;
Line 56, replace "the the" with -- the --.

Signed and Sealed this

Eleventh Day of April, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office